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What is Claimed is:

1. A compound which has the structure

$$\begin{array}{c|c}
R^{2a} & R^{2b} \\
Q & R^{2c} & R^{2c}
\end{array}$$

$$\begin{array}{c|c}
R^{2a} & R^{2c} & R^{2c} \\
R^{2c} & R^{2c} & R^{2c}
\end{array}$$

$$\begin{array}{c|c}
R^{2a} & R^{2c} & R^{2c} \\
R^{2c} & R^{2c} & R^{2c}
\end{array}$$

$$\begin{array}{c|c}
R^{2a} & R^{2c} & R^{2c} \\
R^{2c} & R^{2c} & R^{2c}
\end{array}$$

wherein x is 1,2, 3 or 4; m is 1 or 2; n is 1 or 2;

Q is C or N;

A is O or S;

Z is O or a bond;

R¹ is H or lower alkyl;

X is CH or N;

 $\ensuremath{\mbox{R}^2}$ is H, alkyl, alkoxy, halogen, amino or substituted amino;

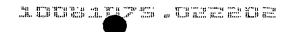
 R^{2a} , R^{2b} and R^{2c} are the same or different and are selected from H, alkyl, alkoxy, halogen, amino or substituted amino;

R³ is H, alkyl, arylalkyl, aryloxycarbonyl, alkyloxycarbonyl, alkynyloxycarbonyl, alkenyloxycarbonyl, arylcarbonyl, alkylcarbonyl, aryl, heteroaryl,

alkyl(halo)aryloxycarbonyl, alkyloxy(halo)aryloxycarbonyl cycloalkylaryloxycarbonyl, cycloalkyloxyaryloxycarbonyl, cycloheteroalkyl, heteroarylcarbonyl, heteroaryl-heteroarylalkyl, alkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, alkoxycarbonylamino,

25 aryloxycarbonylamino, heteroaryloxycarbonylamino, heteroaryl-heteroarylcarbonyl, alkylsulfonyl, alkenylsulfonyl, heteroaryloxycarbonyl, cycloheteroalkyloxycarbonyl, heteroarylalkyl, aminocarbonyl, substituted aminocarbonyl,

alkylaminocarbonyl, arylaminocarbonyl, heteroarylalkenyl, cycloheteroalkylheteroarylalkyl, hydroxyalkyl, alkoxy, alkoxyaryloxycarbonyl, arylalkyloxycarbonyl, alkylaryloxycarbonyl, arylheteroarylalkyl, arylalkylarylalkyl, aryloxyarylalkyl, alkynyloxycarbonyl,



haloalkoxyaryloxycarbonyl, alkoxycarbonylaryloxycarbonyl, aryloxyaryloxycarbonyl, arylsulfinylarylcarbonyl, arylthioarylcarbonyl, alkoxycarbonylaryloxycarbonyl, arylalkenyloxycarbonyl, heteroaryloxyarylalkyl, aryloxyarylcarbonyl, aryloxyarylalkyloxycarbonyl, 5 arylalkenyloxycarbonyl, arylalkylcarbonyl, aryloxyalkyloxycarbonyl arylalkylsulfonyl, arylthiocarbonyl, arylalkenylsulfonyl, hateroarylsulfonyl, arylsulfonyl, alkoxyarylalkyl, heteroarylalkoxycarbonyl, arylheteroarylalkyl, 10 alkoxyarylcarbonyl, aryloxyheteroarylalkyl, heteroarylalkyloxyarylalkyl, arylarylalkyl, arylalkenylarylalkyl, arylalkoxyarylalkyl, arylcarbonylarylalkyl, alkylaryloxyarylalkyl, arylalkoxycarbonylheteroarylalkyl, heteroarylarylalkyl, 15 arylcarbonylheteroarylalkyl, heteroaryloxyarylalkyl, arylalkenylheteroarylalkyl, arylaminoarylalkyl or aminocarbonylarylarylalkyl;

Y is CO_2R^4 (where R^4 is H or alkyl, or a prodrug ester) or Y is a C-linked 1-tetrazole, a phosphinic acid of the structure P(O) (OR^{4a}) R^5 , (where R^{4a} is H or a prodrug ester, R^5 is alkyl or aryl) or a phosphonic acid of the structure P(O) (OR^{4a})₂, (where R^{4a} is H or a prodrug ester);

including all stereoisomers thereof, prodrug esters thereof, and pharmaceutically acceptable salts thereof, with the proviso that where X is CH, A is O, Q is C, Z is O and Y is CO_2R^4 , then R^3 is other than H or alkyl containing 1 to 5 carbons in the normal chain.

2. A compound having the structure

or

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3. The compound as defined in Claim 1 having the structure

$$R^{2a}$$
 R^{2b}
 R^{2a}
 R^{2b}
 R^{2a}
 R^{2b}
 R^{2a}
 R^{2b}
 R^{2a}
 R^{2b}
 R^{2a}
 R^{2b}
 R^{2a}
 R

4. The compound as defined in Claim 1 having structure

$$(CH_2)_x = 0$$

$$(CH_2)_m = 0$$

$$(CH_2)_m = 0$$

$$(CH_2)_m = 0$$

$$(CH_2)_m = 0$$
or

- 5. The compound as defined in Claim 1 wherein $(CH_2) \times is$ alkylene, alkenylene, allenyl, or alkynylene.
- 6. The compound as defined in Claim 4 wherein \boldsymbol{X} is CH.
- 7. The compound as defined in Claim 4 wherein \boldsymbol{X} 20 is \boldsymbol{N} .

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8. The compound as defined in Claim 1 having the structure

wherein R¹ is alkyl, R^{3b} is arylalkylamino, arylarylamino, arylamino, arylamino, alkoxyarylamino, dialkoxyarylamino, dihaloarylamino or alkylthioarylamino.

9. The compound as defined in Claim 1 having the structure

$$(CH_2)_{\pi} O (CH_2)_{n} (CH_2)_{n} - CO_2H$$

10. The compound as defined in Claim 1 wherein R^{2a}

is alkoxy or H, $\begin{array}{c} \text{CH}_3 \\ \text{(CH}_2)_x \text{ is CH}_2, \text{ (CH}_2)_2, \text{ (CH}_2)_3, \text{ or } \\ \hline \\ \text{CH} \\ \end{array} \begin{array}{c} \text{CH}_3 \\ \text{CH}_2 \\ \text{ where } \text{R}_a \text{ is alkyl or alkenyl)}, \text{ (CH}_2)_m \text{ is CH}_2, \text{ R}^1 \\ \text{is lower alkyl, preferably -CH}_3, \text{ R}^2 \text{ is H, R}^{2a} \text{ is H, R}^4 \text{ is} \\ \end{array}$

H, X is CH, and R³ is arylalkyloxycarbonyl, arylheteroarylalkyl, aryloxyarylalkyl, arylalkyl, aryloxycarbonyl,

20 alkoxyaryloxycarbonyl, alkylaryloxycarbonyl, aryloxyaryloxycarbonyl, heteroaryloxyarylalkyl, heteroaryloxycarbonyl, aryloxyarylcarbonyl, arylalkenyloxycarbonyl, cycloalkylaryloxycarbonyl, arylalkylarylcarbonyl, heteroaryl-heteroarylalkyl,

25 cycloalkyloxyaryloxycarbonyl, heteroarylheteroarylcarbonyl, alkyloxyaryloxycarbonyl, arylalkylsulfonyl, arylalkenylsulfonyl, alkoxyarylalkyl, arylthiocarbonyl, cycloheteroalkylalkyloxycarbonyl, cycloheteroalkyloxycarbonyl, or polyhaloalkylaryloxy-

30 carbonyl, which may be optionally substituted.

- 11. The compound as defined in Claim 5 wherein \boldsymbol{X} is CH.
- 5 12. The compound as defined in Claim 5 wherein X is N.
 - 13. The compound as defined in Claim 1 wherein x is 2, m is 1, and n is 1.
 - 14. The compound as defined in Claim 1 having the structure

$$\begin{array}{c|c} & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & \\ & & & \\ &$$

15. The compound as defined in Claim 1 having the structure

where
$$(CH_2)_n$$
 is CH_2 or CH_2

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16. The compound as defined in Claim 1 having the structure

$$\begin{array}{c} Ph \\ \longrightarrow N \\ CH_3 \end{array} \qquad \begin{array}{c} N \\ \longrightarrow CO_2H \\ \longrightarrow CH_3 \end{array} \qquad \begin{array}{c} Ph \\ \longrightarrow N \\ \longrightarrow CH_3 \end{array} \qquad \begin{array}{c} CO_2H \\ \longrightarrow CH_3 \end{array}$$

$$\begin{array}{c} Ph \\ O \\ CH_3 \end{array}$$

Ph
$$CO_2H$$
 CH_3
 R^3
 CO_2H
 CH_3
 R^3
 R^3

, where $R^3 =$

15

5

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$$N$$
 CO_2H R^{3c} , where R^{3c} =

(S)
$$-CH_3$$
, (R) $-CH_3$, (R) (R) (R)

$$\mathbb{R}^{3d}$$
 \mathbb{R}^{3d}
 \mathbb{R}^{3d}

CI, CH₃, CH₃

Ph
$$CO_2H$$
 CO_2H CO_2H

10

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CH₃

CH

$$CH_3$$
 N CO_2H R^{3e} , where R^{3e} =

15

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. 5 10

where R^{3f} =

$$CH_3$$
 CO_2H , where R^{3f} =

15

5

$$\begin{array}{c} Ph \\ \\ CH_3 \end{array} \\ \begin{array}{c} O \\ O \\ \\ CH_3 \end{array} \\ \begin{array}{c} O \\ O \\ \\ CH_3 \end{array} \\ \begin{array}{c} O \\ O \\ \\ CO_2H \\ \\ \end{array} \\ \begin{array}{c} F \\ \\ O \\ \\ CO_2H \\ \end{array} \\ \end{array}$$

$$CH_3$$
 CH_3
 R^{3g}
 CO_2H
, where $R^{3g} =$

Ph
$$CO_2H$$
 O_2S R^{3g} where R^{3g} =

, LO , H³C CH³ CH³ 10 where $R^3 =$ 15

where $R^3 =$

$$\begin{array}{c}
\mathsf{Ph} \\
\mathsf{O} \\
\mathsf{CH}_{3}
\end{array}$$

where R³ =

15

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CH₃

CH₃

CH₃

CH₄

CH₃

CH₄

CH₅

CH₅

CH₆

CH₇

CH

where $R^a = (\pm) - Me$, (\pm) n-Bu,

Ph CH₃ N CO₂H

OCH₂

where $R^a = (\pm)$ Et, (\pm) i-Bu,

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осн₃ ọcH₃ ọCH₃ CH₃ ←CH₃ CO₂H ĒH₃ Ė́H₃

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$$\begin{array}{c} \text{OCH}_3\\ \\ \text{OO}\\ \\ \text{OO}\\ \\ \text{CH}_3 \end{array}$$

OCH₃

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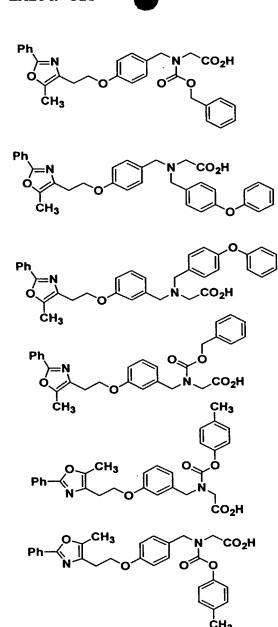
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$$Ph \stackrel{O \longrightarrow CH_3}{\longrightarrow} O \stackrel{O}{\longrightarrow} O$$

$$N \longrightarrow CO_2H$$

17. The compound as defined in Claim 1 having the structure



$$\begin{array}{c} Ph \\ CH_{3} \end{array}$$

$$\begin{array}{c} Ph \\ CH_{3} \end{array}$$

$$\begin{array}{c} Ph \\ CH_{3} \end{array}$$

$$\begin{array}{c} Ph \\ CO_{2}H \end{array}$$

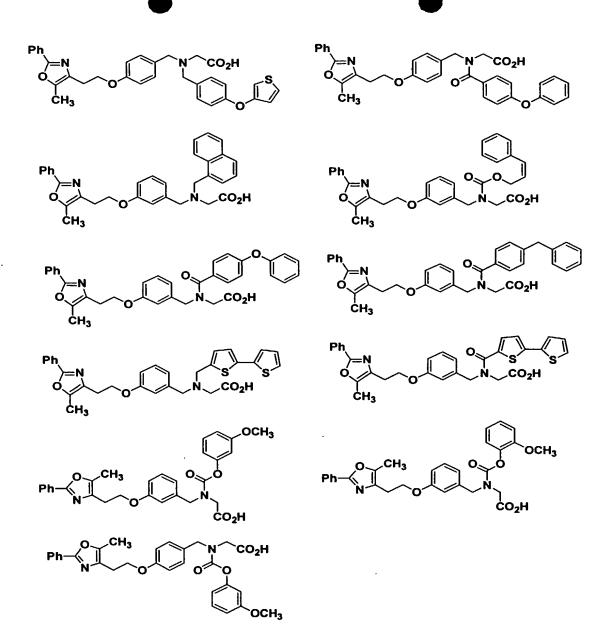
$$\begin{array}{c} CO_{2}H \\ CH_{3} \end{array}$$

$$\begin{array}{c} Ph \\ CO_{2}H \end{array}$$

$$\begin{array}{c} CO_{2}H \\ CH_{3} \end{array}$$

$$\begin{array}{c} CO_{2}H \\ CH_{3} \end{array}$$

$$\begin{array}{c} CO_{2}H \\ CH_{3} \end{array}$$



$$\begin{array}{c} Ph \\ O \\ CH_3 \end{array}$$

$$\begin{array}{c} Ph \\ O \\ CH_3 \end{array}$$

$$\begin{array}{c} Ph \\ O \\ CH_3 \end{array}$$

$$\begin{array}{c} Ph \\ O \\ CO_2H \end{array}$$

$$\begin{array}{c} Ph \\ O \\ CO_2H \end{array}$$

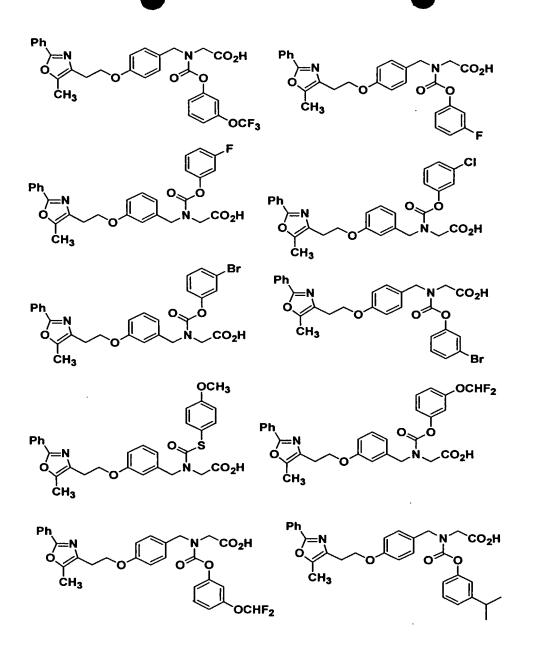
$$\begin{array}{c} Ph \\ O \\ CH_3 \end{array}$$

$$\begin{array}{c} Ph \\ O \\ CO_2H \end{array}$$

$$\begin{array}{c} Ph \\ O \\ CH_3 \end{array}$$

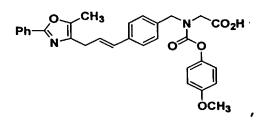
$$\begin{array}{c} Ph \\ O \\ CO_2H \end{array}$$

$$\begin{array}{c} Ph \\ O \\ CH_3 \end{array}$$



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18. The compound as defined in Claim 1 having the structure $\ensuremath{\mathsf{Structure}}$



\$19.\$ The compound as defined in Claim 1 having the \$5\$ structure

 $\,$ 20. The compound as defined in Claim 1 having the $\,$ 10 $\,$ structure

$$\begin{array}{c} Ph \\ CH_{3} \end{array} \qquad \begin{array}{c} Ph \\ CO_{2}H \end{array} \qquad \begin{array}{c} Ph \\ CH_{3} \end{array} \qquad \begin{array}{c} Ph \\ PH_{3} \end{array} \qquad \begin{array}{c} PH_{3} \end{array} \qquad \begin{array}{c} PH_{3} \end{array} \qquad \begin{array}{c} PH_{3} \end{array} \qquad \begin{array}{c} PH_{3} \end{array} \qquad \begin{array}{c}$$

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Ph_N O O

$$\begin{array}{c|c} Ph & & & \\ \hline O & & & \\ \hline O & & & \\ \hline CH_3 & & & \\ \end{array}$$

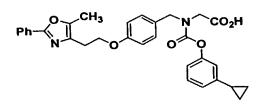
$$\begin{array}{c|c} Ph & O & S & S \\ \hline O & N & CO_2H \\ \hline CH_3 & \end{array}$$

$$\begin{array}{c|c} & & & & \\ & & & & \\ Ph & & & & \\ N & & & & \\ \hline \end{array}$$

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$$Ph \xrightarrow{O \xrightarrow{CH_3}} O \xrightarrow{O} O \\ N \xrightarrow{CO_2H}$$

$$\begin{array}{c|c} \mathsf{Ph} & \mathsf{CH_3} & \mathsf{CO_2H} \\ \mathsf{N} & \mathsf{O} & \mathsf{O} & \mathsf{O} \\ \mathsf{N} & \mathsf{O} & \mathsf{O} & \mathsf{O} \\ \mathsf{O} & \mathsf{O} & \mathsf{O} \\ \mathsf{OCH_3} & \mathsf{O} & \mathsf{O} \\ \end{array}$$



$$\mathsf{Ph} \overset{\mathsf{O} \longrightarrow \mathsf{CH}_3}{\underset{\mathsf{O}}{\bigvee}} \mathsf{O} \overset{\mathsf{N} \longrightarrow \mathsf{CO}_2\mathsf{H}}{\underset{\mathsf{O}}{\bigvee}}$$

$$\begin{array}{c|c} O & CH_3 & N \\ \hline O & O \\ \hline$$

$$Ar = CI \longrightarrow F_{3}C \longrightarrow F_{3}C$$

$$Ar = CI \longrightarrow F_3C \longrightarrow F_3C$$

21. The compound as defined in Claim 1 having the $5\,$ structure

22. The compound as defined in Claim 1 having the structure

10

23. The compound as defined in Claim 1 having the structure

24. The compound as defined in Claim 1 having the structure

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25. The compound as defined in Claim 1 having the structure

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26. The compound as defined in Claim 1 having the structure

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27. The compound as defined in Claim 1 having the structure

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28. The compound as defined in Claim 1 having the structure

10 29. The compound as defined in Claim 1 having the structure

30. The compound as defined in Claim 1 having the

15 structure

31. The compound as defined in Claim 1 having the structure

$$\begin{array}{c|c} \text{Ph} & \text{CH}_3 \\ \text{N} & \text{CO}_2\text{H} \\ \\ \text{OCH}_3 \end{array}$$

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32. The compound as defined in Claim 1 having the structure

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33. A pharmaceutical composition comprising a compound as defined in Claim 1 and a pharmaceutically acceptable carrier therefor.

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34. A method for lowering blood glucose levels which comprises administering to a patient in need of treatment a therapeutically effective amount of a compound as defined in Claim 1.

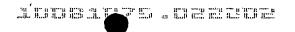
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35. A method for treating diabetes which comprises administering to a patient in need of treatment a therapeutically effective amount of a compound as

defined in Claim 1.

36. A method for treating a premalignant disease, an early malignant disease, a malignant disease, or a dysplastic disease, which comprises administering to a patient in need of treatment a therapeutically effective amount of a compound as defined in Claim 1.



- 37. A pharmaceutical combination comprising a compound as defined in Claim 1 and a lipid-lowering agent, a lipid modulating agent, an antidiabetic agent, an anti-obesity agent, an antihypertensive agent, a platelet aggregation inhibitor, and/or an antiosteoporosis agent.
- 38. The pharmaceutical combination as defined in Claim 37 comprising said compound and an antidiabetic agent.
- 39. The combination as defined in Claim 38 wherein the antidiabetic agent is 1, 2, 3 or more of a biguanide, a sulfonyl urea, a glucosidase inhibitor, a PPARα
 15 agonist, a PPAR γ agonist, a PPAR α/γ dual agonist, an SGLT2 inhibitor, a DP4 inhibitor, an aP2 inhibitor, an insulin sensitizer, a glucagon-like peptide-l (GLP-l), insulin and/or a meglitinide.
- 40. The combination as defined in Claim 39 wherein the antidiabetic agent is 1, 2, 3 or more of metformin, glyburide, glimepiride, glipyride, glipizide, chlorpropamide, gliclazide, acarbose, miglitol, pioglitazone, troglitazone, rosiglitazone, insulin, Gl-25 262570, isaglitazone, JTT-501, NN-2344, L895645, YM-440, R-119702, AJ9677, repaglinide, nateglinide, KAD1129, AR-HO39242, GW-409544, KRP297, AC2993, LY315902, P32/98 and/or NVP-DPP-728A.
- 30 41. The combination as defined in Claim 38 wherein the compound is present in a weight ratio to the antidiabetic agent within the range from about 0.001 to about 100:1.
- 35 42. The combination as defined in Claim 37 wherein the anti-obesity agent is a beta 3 adrenergic agonist, a lipase inhibitor, a serotonin (and dopamine) reuptake

inhibitor, a thyroid receptor agonist, an aP2 inhibitor and/or an anorectic agent.

- 43. The combination as defined in Claim 42 wherein the anti-obesity agent is orlistat, ATL-962, AJ9677, L750355, CP331648, sibutramine, topiramate, axokine, dexamphetamine, phentermine, phenylpropanolamine, and/or mazindol.
- 10 44. The combination as defined in Claim 37 wherein the lipid lowering agent is an MTP inhibitor, an HMG CoA reductase inhibitor, a squalene synthetase inhibitor, a fibric acid derivative, an upregulator of LDL receptor activity, a lipoxygenase inhibitor, or an ACAT inhibitor.
- 45. The combination as defined in Claim 44 wherein the lipid lowering agent is pravastatin, lovastatin, simvastatin, atorvastatin, cerivastatin, fluvastatin, itavastatin, visastatin, fenofibrate, gemfibrozil, clofibrate, avasimibe, TS-962, MD-700, cholestagel, niacin and/or LY295427.
- 46. The combination as defined in Claim 44 wherein the compound is present in a weight ratio to the lipid25 lowering agent within the range from about 0.001:1 to about 100:1.
- 47. The combination as defined in Claim 37 wherein the antihypertensive agent is an ACE inhibitor, angiotensin II receptor antagonist, NEP/ACE inhibitor, calcium channel blocker and/or β -adrenergic blocker.
- 48. The combination as defined in Claim 47 wherein the antihypertensive agent is an ACE inhibitor which is captopril, fosinopril, enalapril, lisinopril, quinapril, benazepril, fentiapril, ramipril or moexipril; an NEP/ACE inhibitor which is omapatrilat, [S[(R*,R*)]-hexahydro-6-

[(2-mercapto-1-oxo-3-phenylpropyl)amino]-2,2-dimethyl-7-oxo-1H-azepine-1-acetic acid (gemopatrilat) or CGS 30440;

an angiotensin II receptor antagonist which is irbesartan, losartan or valsartan;

amlodipine besylate, prazosin HCl, verapamil, nifedipine, nadolol, propranolol, carvedilol, or clonidine HCl.

- 49. The combination as defined in Claim 37 wherein the platelet aggregation inhibitor is aspirin, clopidogrel, ticlopidine, dipyridamole or ifetroban.
- 50. A method for treating insulin resistance, hyperglycemia, hyperinsulinemia, or elevated blood levels of free fatty acids or glycerol, hyperlipidemia, obesity, Syndrome X, dysmetabolic syndrome, inflammation, diabetic complications, impaired glucose homeostasis, impaired glucose tolerance, hypertriglyceridemia or atherosclerosis which comprises administering to a mammalian species in need of treatment a therapeutically effective amount of a pharmaceutical combination as defined in Claim 43.
- 51. A method for treating irritable bowel

 25 syndrome, Crohn's disease, gastric ulceritis or osteroporosis, or psoriasis, which comprises administering to a mammalian species in need of treatment a therapeutically effective amount of a compound as defined in Claim 1.

- 52. The method as defined in Claim 36 wherein the disease is a liposarcoma or an epithelial tumor.
- 53. The method as defined in Claim 52 wherein the epithelial tumor is a tumor of the breast, prostate, colon, ovaries, stomach or lung.

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54. The method as defined in Claim 36 wherein the disease is ductal carcinoma in situ of the breast, lobular carcinoma in situ of the breast, fibroadenoma of the breast, or prostatic intraepithelial neoplasia.